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PATENT SPECIFICATION

NO DRAWINGS

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841524

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International Classification:—C07d.

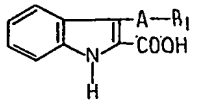
COMPLETE SPECIFICATION

Improvements in or relating to Indole Derivatives

We, MAY & BAKER LIMITED, a British Company of Dagenham, Essex, England, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention is for improvements in or relating to indole derivatives and has for its object the provision of new indole derivatives which are useful intermediates for the preparation of therapeutically active substances.

The new indole derivatives of the present invention are the 3 - alkylindole - 2 - carboxylic acids of the general formula:



wherein A represents a straight or branched saturated hydrocarbon chain containing not more than 6 carbon atoms, and R_1 represents a mono - acylamino group which may be derived from an aliphatic, aromatic or heterocyclic mono- or dicarboxylic acid, the benzene ring of the indole nucleus being substituted by one or more alkoxy, aryloxy, or aralkoxy groups. Preferably A represents a straight or branched saturated hydrocarbon chain having not more than 2 carbon atoms between the indole nucleus and the group R_1, R_1 represents a phthaloylamino group, and the benzene ring of the indole nucleus is substituted by one or more benzyloxy and/or methoxy groups, said group or one of said groups preferably being in the 5-position.

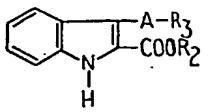
These new derivatives are of importance primarily as intermediates in the preparation of 3 - aminoalkylindoles into which they are converted by decarboxylation, which is readily achieved by heating, followed, if necessary, by conversion of the group R_1 into an amino group. When the benzene ring of the indole nucleus is substituted by an alkoxy or aralkoxy group such a group may be converted into a hydroxy group if desired.

The 3 - aminoalkylindoles which may thus be prepared from the new indole derivatives of the present invention include 3 - β - aminoethyl - 5 - hydroxyindole (5 - hydroxytryptamine), otherwise known as serotonin, and its analogues such as 3 - (β - aminopropyl) - 5-hydroxyindole which possess valuable pharmacological properties having, for example, haemostatic activity or being effective in the regulation of vascular tone and blood-pressure or of kidney activity, or in the restoration or maintenance of normal mental activity.

Among the preferred new indole derivatives is 5 - benzyloxy - 3 - β - (*o* - carboxybenzamido)ethylindole - 2 - carboxylic acid which is a particularly valuable intermediate for the preparation of serotonin to which it may be converted as follows: the said intermediate is first decarboxylated, for example by heating to 240—250° C., to form 5 - benzyloxy - 3 - (β - phthalimidoethyl) - indole which is then treated with hydrazine to form 3 - β - aminoethyl - 5 - benzyloxyindole (5 - benzyloxytryptamine) isolated as its sulphate. Finally, the benzyl group is removed by hydrogenation to yield the sulphate of serotonin. This novel process for the preparation of serotonin has been found to possess considerable practical advantages over the methods previously known and described in the literature.

According to a feature of the present invention, the new 3 - alkyl - indole - 2 - carboxylic acids of the foregoing general formula may be prepared by the hydrolysis of esters of the general formula:

[*Price 3s. 6d.*]



wherein R_2 represents a hydrocarbon radical, R_3 represents the radical R_1 as hereinbefore defined or a phthalimido group, and A is as hereinbefore defined, and the benzene ring is substituted as aforesaid, the conditions of hydrolysis being such as to preserve, or form when R_3 is a phthalimido group, a group —A—R_1 in the 3-position. When the group R_3 is a phthalimido group, the ester group may readily be hydrolysed under alkaline conditions, for example by heating with alcoholic potassium hydroxide, the phthalimido group being converted to a phthaloylamino group which is not removed.

The ester starting materials may be prepared from the corresponding aniline and an appropriately substituted α - (alkyl)acetoacetic ester in a manner similar to that described by Keimatsu and Sugasawa (J. Pharm. Soc. Japan, 1928, *48*, 762).

The invention is illustrated by the following Examples:

EXAMPLE I

p - Benzyloxyaniline (Boehme, W. F. J. Amer. Chem. Soc., 1953, *75*, 2502) (150 g.) is dissolved in boiling ethanol (300 ml.) and to this hot solution is added as rapidly as possible a mixture of hydrochloric acid (300 ml.) and water (450 ml.) followed by crushed ice (600 g.). To the stirred suspension is added sodium nitrite (68 g.) in water (150 ml.) over about 20 minutes and the suspension is then stirred for a further 40 minutes, the temperature being maintained at 5—10° C. by external cooling. The solution of diazotised *p* - benzyloxyaniline is treated with charcoal and filtered.

Ethyl α - acetyl - ε - phthalimidovalerate (Keimatsu and Sugasawa, *ibid.*) (237 g.) is dissolved in warm ethanol (1100 ml.). To the cooled solution is added anhydrous sodium acetate (615 g.) and crushed ice (500 g.). To the stirred mixture is added rapidly the filtered solution of diazotised *p* - benzyloxyaniline described above, and the reaction mixture is stirred while allowing it to attain room temperature. The red viscous oil which separates is extracted with benzene (3 × 450 ml.), the combined benzene extracts dried (Na_2SO_4), and the benzene removed by distillation. The crude phenylhydrazone obtained is dissolved in dry ethanol (1600 ml.) and the stirred solution saturated at the boiling point with a rapid stream of hydrogen chloride gas. After cooling in ice, the solid formed is filtered off, washed with ice-cold ethanol (2 × 400 ml.) and then with water (2 × 400 ml.) and dried at 80° C. Ethyl - 5 - benzyloxy - 3 - (β - phthalimidoethyl) indole - 2 - carboxylate (178 g., 51% yield) is obtained as almost colourless small needles, m.p. 189—191° C.

The last mentioned product (135 g.) is suspended in ethanol (500 ml.). Potassium hydroxide (158 g.) in water (1.8 litres) is added, the mixture is warmed on the steam bath until solution is complete (15 minutes) and maintained at refluxing temperature for 1½ hours. The bulk of the ethanol is then removed by distillation, the residue is cooled to 10° C., acidified with 4N hydrochloric acid and allowed to stand. The solid which separates is filtered off, washed with water until free of hydrochloric acid and dried at 80° C. 5-Benzyloxy - 3 - β - (*o* - carboxybenzamido)ethylindole - 2 - carboxylic acid (129 g., 98% yield) is obtained as an almost colourless solid which melts with decomposition at 230—235° C. with prior dehydration at about 200° C.

The last mentioned product may be converted to serotonin (isolated as the creatinine sulphate) as follows:

5 - Benzyloxy - 3 - β - (*o*- carboxybenzoamido)ethylindole - 2 - carboxylic acid (100 g.) is gently melted with stirring in a flask heated by an oil bath up to about 250° C., the evolved carbon dioxide and water being removed by a stream of nitrogen. Decarboxylation is complete in about 1½ hours. The residue, which on cooling solidifies to a glassy solid, is dissolved in hot methyl ethyl ketone (about 1 litre) and a small quantity of insoluble material is removed by filtration. The filtrate is concentrated to about 300 ml. and hot ethanol (900 ml.) is added. The solid which crystallises on cooling is filtered off and washed with cold ethanol (100 ml.). A second crop is obtained by concentrating the liquors. The two crops are combined, suspended in cold N-sodium hydroxide, filtered off and washed first with water and then with cold ethanol. 5 - Benzyloxy - 3 - (β - phthalimidoethyl)indole (73 g., 84% yield) is obtained as pale yellow prisms, m.p. about 179—181° C.

5 - Benzyloxy - 3 - (β - phthalimidoethyl)-indole (32.5 g.), hydrazine hydrate 80% (15.5 ml.) and ethanol (850 ml.) are refluxed together for 2½ hours. The solution so obtained is evaporated to dryness on a steam bath, using reduced pressure for the final stages. 2N Sodium hydroxide (250 ml.) is added to the residue whilst still warm. Ether (400 ml.) is added and the whole cooled in ice until a solid separates. After removal of this solid by filtration through Hyflo (registered Trade Mark), the ether layer is separated from the filtrate which is further extracted with ether (100 ml.). The combined ethereal solutions are washed with water until the washings are neutral and then extracted with N acetic acid (150 ml.) and with water (50 ml.). The combined aqueous layers are washed with ether (50 ml.) and made strongly acid by the dropwise addition of concentrated sulphuric acid.

Crude 5 - benzyloxytriptamine sulphate (22.8 g., 83% yield) is filtered off, washed with ice cold water until the washings are neutral and recrystallised from water (250 ml.) incorporating a charcoal treatment. 5 - Benzyloxytryptamine sulphate monohydrate (20 g., 73% yield) is obtained as almost colourless plates, m.p. 187—189° C. (evacuated sealed tube).

Palladium chloride (0.42 g.) and acid washed charcoal (2.1 g.) are suspended in water (120 ml.) and hydrogenated at room temperature and atmospheric pressure until no further uptake occurs. A suspension of 5 - benzyloxytryptamine sulphate monohydrate (11.6 g.) in ethanol (180 ml.) is added and the resulting suspension is hydrogenated under similar conditions. An uptake of 117% of the theoretical value occurs. The catalyst and charcoal are removed by filtration through Hyflo and the filtrate evaporated to a thick syrup under reduced pressure in an atmosphere of nitrogen. The syrup is dissolved in a solution of creatinine sulphate hemihydrate (5.95 g.) in hot water (35 ml.) and to this solution is added hot acetone (250 ml.). The solid which separates is filtered off, washed with acetone and dried at 80° C. to give crude serotonin creatinine sulphate (13 g., 93% yield), m.p. 217—219° C. (sealed evacuated tube). This material is combined with two similar batches (35.8 g. in all) and the whole recrystallised twice by dissolving in hot water (300 ml.), filtering (charcoal) and adding ethanol (200 ml.). Serotonin creatinine sulphate monohydrate (25.5 g., 67% yield) crystallises on standing as almost colourless microprisms, m.p. 219—221° C. with decomposition (sealed evacuated tube).

EXAMPLE II

In a manner similar to that described in Example I, 3:4:5 - trimethoxyaniline (Hughes *et al*, Aust. J. Sci. Res. 1950, *3A*, 497) (36.6 g.) and ethyl α - acetyl - δ - phthalimidovalerate (70.0 g.) are converted to ethyl 4:5:6-trimethoxy - 3 - (β -phthalimidoethyl)indole-2 - carboxylate (42.0 g., 47% yield) (light brown prisms from methyl ethyl ketone, m.p. 204—206° C.) which is then hydrolysed (22.6 g.) to 4:5:6 - trimethoxy - 3 - β - (*o* - carboxybenzamido)ethylindole - 2 - carboxylic acid.

The last mentioned product may be decarboxylated without purification to give 4:5:6-trimethoxy - 3 - (β - phthalimidoethyl)indole (12.0 g., 63% yield based on the phthalimidoethyl ester) (yellow needles from ethanol, m.p. 175—177° C.) which is then converted into 4:5:6 - trimethoxytryptamine which on treatment in ethanolic solution with 2N sulphuric acid gives the sulphate (colourless prisms from aqueous ethanol, m.p. 255—256° C. in a sealed evacuated tube) in a yield of 68% of theory.

EXAMPLE III

In a manner similar to that described in Example I, *p* - anisidine (24.6 g.) and ethyl α - acetyl - δ - phthalimidovalerate (69.6 g.) are converted to ethyl 5 - methoxy - 3 - (β-phthalimidoethyl)indole - 2 - carboxylate (12.2 g., 17% yield) (orange powder, m.p. 238—240° C.) which is then hydrolysed (11.1 g.) to give 5 - methoxy - 3 - β - (*o* - carboxybenzoamido)ethylindole - 2 - carboxylic acid (10.6 g., 98% yield), (cream coloured powder, m.p. 244—250° C. with dehydration at 230° C.).

The last mentioned product (10.6 g.) may be decarboxylated to 5 - methoxy - 3 - (β-phthalimidoethyl)indole (7.6 g., 85.5% yield) (yellow needles from carbon tetrachloride, m.p. 156—158° C.) which is then converted (6.40 g.) to 5 - methoxytryptamine (2.35 g., 66% yield) (colourless prisms from aqueous methanol, m.p. 120—121° C.). The corresponding sulphate obtained as colourless prisms from aqueous ethanol melts at 230—232° C. in a sealed evacuated tube.

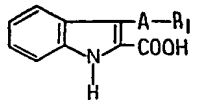
EXAMPLE IV

In a manner similar to that described in Example I, *m* - benzyloxyaniline (Morton and Slaunwhite J. Biol Chem. *179*, 259 (1949)) (19.9 g.) and ethyl α - acetyl - δ - phthalimidovalerate (31.7 g.) are converted to ethyl 6-benzyloxy - 3 - (β - phthalimidoethyl)indole-2 - carboxylate (15.5 g., 33% yield) (fawn plates from toluene, m.p. 199—201° C.) which is then hydrolysed (7.6 g.) to 6 - benzyloxy-3 - β - (*o* - carboxybenzamido)ethylindole - 2-carboxylic acid.

The last mentioned product may be decarboxylated without purification to give 6-benzyloxy - 3 - (β - phthalimidoethyl)indole (5 g., 77% yield based on the phthal - imidoethyl ester) (yellow prisms from toluene, m.p. 203—205° C.) which is then converted (4.5 g.) to 6 - benzyloxytryptamine. This, on treatment with sulphuric acid, gives the sulphate (1.7 g., 50% yield) (colourless plates from water, m.p. 296—297° C. (decomp.) in a sealed evacuated tube). Catalytic debenzylation of this sulphate (1.4 g.) gives 6 - hydroxytryptamine sulphate isolated as the creatinine sulphate complex (0.9 g.) (colourless needles from ethanol, m.p. 210—211° C. in a sealed evacuated tube).

WHAT WE CLAIM IS:—

1. 3 - Alkylindole - 2 - carboxylic acids of the general formula:



wherein A represents a straight or branched saturated hydrocarbon chain containing not more than 6 carbon atoms, R_1 represents a mono - acylamino group which may be derived from an aliphatic or aromatic or heterocyclic mono- or dicarboxylic acid, and the

benzene ring carries one or more substituents selected from alkoxy, aryloxy and aralkoxy groups.

2. Indole derivatives as claimed in claim 1 wherein A represents a straight or branched saturated hydrocarbon chain having not more than 2 carbon atoms between the indole nucleus and the group R_1, R_1 represents a phthaloylamino group, and the benzene ring of the indole nucleus is substituted by one or more benzyloxy and/or methoxy groups.

3. Indole derivatives as claimed in claim 2 wherein the, or one of the, benzene ring substituent(s) is in the 5-position.

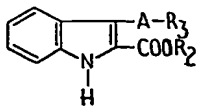
4. 5 - Benzyloxy - 3 - β - (*o* - carboxybenzamido)ethylindole - 2 - carboxylic acid.

5. 4:5:6 - Trimethoxy - 3 - β - (*o* - carboxybenzamido)ethylindole - 2 - carboxylic acid.

6. 5 - Methoxy - 3 - β - (*o* - carboxybenzamido)ethylindole - 2 - carboxylic acid.

7. 6 - Benzyloxy - 3 - β - (*o* - carboxybenzamido)ethylindole - 2 - carboxylic acid.

8. Process for the preparation of indole derivatives as claimed in claims 1 to 7 which comprises the hydrolysis of esters of the general formula:



wherein R_2 represents a hydrocarbon radical and R_3 represents the radical R_1 as defined in claim 1 or a phthalimido group, A is as defined in claim 1, and the benzene ring carries one or more substituents selected from alkoxy, aryloxy and aralkoxy groups, the conditions of hydrolysis being such as to preserve, or form when R_3 is a phthalimido group, a group —A—R_1 in the 3-position.

9. Process as claimed in claim 8 wherein the group R_3 is a phthalimido group and hydrolysis is effected under alkaline conditions.

10. Process as claimed in claim 9 wherein the hydrolysis is effected by heating with alcoholic potassium hydroxide.

11. Process as claimed in any one of claims 8 to 10 when carried out substantially as described in any one of the foregoing Examples.

J. A. KEMP & CO.,
Chartered Patent Agents,
9, Staple Inn, London, W.C.1.

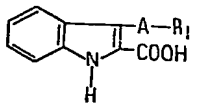
PROVISIONAL SPECIFICATION

Improvements in or relating to Indole Derivatives

We, MAY & BAKER LIMITED, a British Company, of Dagenham, in the County of Essex, England, do hereby declare this invention to be described in the following statement:—

This invention is for improvements in or relating to indole derivatives and has for its object the provision of new indole derivatives which are useful intermediates for the preparation of therapeutically active substances.

The new indole derivatives of the present invention are the 3 - alkylindole - 2 - carboxylic acids of the general formula:



wherein A represents a straight or branched saturated hydrocarbon chain containing not more than 6 carbon atoms, and R_1 represents a mono - acylamino group which may be derived from an aliphatic, aromatic or heterocyclic mono- or di-carboxylic acid, the benzene ring of the indole nucleus being substituted by one or more alkoxy, aryloxy or aralkoxy groups. Preferably A represents a straight or branched saturated hydrocarbon chain having not more than two carbon atoms between the indole nucleus and the group R_1, R_1 represents a phthaloylamino group and the benzene ring of the indole nucleus is substituted by one or more benzyloxy and/or methoxy groups, said group or one of said groups preferably being in the 5-position.

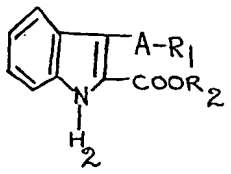
These new derivatives are of importance primarily as intermediates in the preparation of 3 - aminoalkylindoles into which they are converted by decarboxylation, which is readily achieved by heating, followed, if necessary, by conversion of the group R_1 into an amino group. When the benzene ring of the indole nucleus is substituted by an alkoxy or aralkoxy group such a group may be converted into a hydroxy group if desired.

The 3 - aminoalkylindoles which may thus be prepared from the new indole derivatives of the present invention include 3 - β - aminoethyl - 5 - hydroxyindole (5 - hydroxytryptamine), otherwise known as serotonin, and its analogues such as 3 - (β - aminopropyl) - 5-hydroxyindole possess valuable pharmacological properties having, for example, haemostatic activity or being effective in the regulation of vascular tone and blood-pressure or of kidney activity, or in the restoration or maintenance of normal mental activity.

Among the preferred new indole derivatives is 5 - benzyloxy - 3 - β - (*o* - carboxybenzamido)ethylindole - 2 - carboxylic acid which is a particularly valuable intermediate for the preparation of serotonin to which it may be converted as follows: the said intermediate is first decarboxylated, for example by heating to 240—250° C., to form 5 - benzyloxy - 3-

(β - phthalimidoethyl) - indole which is then treated with hydrazine to form 3 - β - aminoethyl - 5 - benzyloxyindole (5 - benzyloxytryptamine) isolated as its sulphate. Finally, the benzyl group is removed by hydrogenation to yield the sulphate of serotonin. This novel process for the preparation of serotonin has been found to possess considerable practical advantages over the methods previously known and described in the literature.

According to a feature of the present invention the new 3 - alkylindole - 2 - carboxylic acids of the foregoing general formula may be prepared by the hydrolysis of esters of the general formula:



wherein R_2 represents a hydrocarbon radical, A and R_1 are as hereinbefore defined, and the benzene ring is substituted as aforesaid, the condition of hydrolysis being such as to preserve a group —A—R_1 in the 3-position. When the group R_1 is a phthalimido group, the ester group may readily be hydrolysed under alkaline conditions, for example by heating with alcoholic potassium hydroxide, the phthalimido group being converted to a phthaloylamino group which is not removed.

The ester starting materials may be prepared from the corresponding aniline and an appropriately substituted α - (alkyl)acetoacetic ester in a manner similar to that described by Keimatsu and Sugasawa (J. Pharm. Soc. Japan, 1928, *48*, 762).

EXAMPLE I

p-Benzyloxyaniline (Boehme, W. F. J. Amer. Chem. Soc., 1953, *75*, 2502) (150 g.) is dissolved in boiling ethanol (300 ml.) and to this hot solution is added as rapidly as possible a mixture of hydrochloric acid (300 ml.) and water (450 ml.) followed by crushed ice (600 g.). To the stirred suspension is added sodium nitrite (68 g.) in water (150 ml.) over about 20 minutes and the suspension is then stirred for a further 40 minutes, the temperature being maintained at 5—10° C. by external cooling. The solution of diazotised *p* - benzyloxyaniline is treated with charcoal and filtered.

Ethyl α - acetyl - δ - phthalimidovalerate (Keimatsu & Sugasawa, *ibid*) (237 g.) is dissolved in warm ethanol (1100 ml.). To the cooled solution is added anhydrous sodium acetate (615 g.) and crushed ice (500 g.). To the stirred mixture is added rapidly the filtered solution of diazotised *p* - benzyloxyaniline described above, and the reaction mixture is stirred while allowing it to attain room temperature. The red viscous oil which separates is extracted with benzene (3 × 450 ml.), the combined benzene extracts dried (Na_2SO_4), and the benzene removed by distillation. The crude phenylhydrazone obtained is dissolved in dry ethanol (1600 ml.) and the stirred solution saturated at the boiling point with a rapid stream of hydrogen chloride gas. After cooling in ice, the solid formed is filtered off, washed with ice-cold ethanol (2 × 400 ml.) and then with water (2 × 400 ml.) and dried at 80° C. Ethyl 5 - benzyloxy - 3 - (β-phthalimidoethyl) - indole - 2 - carboxylate (178 g., 51% yield) is obtained as almost colourless small needles, m.p. 189—191° C.

The last mentioned product (135 g.) is suspended in ethanol (500 ml.). Potassium hydroxide (158 g.) in water (1.8 litres) is added, the mixture is warmed on the steam bath until solution is complete (15 minutes) and maintained at refluxing temperature for 1½ hours. The bulk of the ethanol is then removed by distillation, the residue is cooled to 10° C., acidified with 4N hydrochloric acid and allowed to stand. The solid which separates is filtered off, washed with water until free of hydrochloric acid and dried at 80° C. 5-Benzyloxy - 3 - β - (o - carboxybenzamido)ethylindole - 2 - carboxylic acid (129 g., 98% yield) is obtained as an almost colourless solid which melts with decomposition at 230—235° C. with prior dehydration at about 200° C.

The last mentioned product may be converted to serotonin (isolated as the creatinine sulphate) as follows:

5 - Benzyloxy - 3 - (*o* - carboxybenzamido)-ethylindole - 2 - carboxylic acid (100 g.) is gently melted with stirring in a flask heated by an oil bath up to about 250° C., the evolved carbon dioxide and water being removed by a stream of nitrogen. Decarboxylation is complete in about 1½ hours. The residue, which on cooling solidifies to a glassy solid, is dissolved in hot methyl ethyl ketone (about 1 litre) and a small quantity of insoluble material is removed by filtration. The filtrate is concentrated to about 300 ml. and hot ethanol (900 ml.) is added. The solid which crystallises on cooling is filtered off and washed with cold ethanol (100 ml.). A second crop is obtained by concentrating the liquors. The two crops are combined, suspended in cold N-sodium hydroxide, filtered off and washed first with water and then with cold ethanol. 5 - Benzyloxy - 3 - (β - phthalimidoethyl)indole (73 g., 84% yield) is obtained as pale yellow prisms, m.p. about 179—181° C.

5 - Benzyloxy - 3 - (β - phthalimidoethyl)-indole (32.5 g.), hydrazine hydrate 80% (15.5 ml.) and ethanol (850 ml.) are refluxed together for 2½ hours. The solution so obtained is evaporated to dryness on a steam bath, using reduced pressure for the final stages. 2N

Sodium hydroxide (250 ml.) is added to the residue whilst still warm. Ether (400 ml.) is added and the whole cooled in ice until a solid separates. After removal of this solid by filtration through Hyflo (registered Trade Mark), the ether layer is separated from the filtrate which is further extracted with ether (100 ml.). The combined ethereal solutions are washed with water until the washings are neutral and then extracted with N acetic acid (150 ml.) and with water (50 ml.). The combined aqueous layers are washed with ether (50 ml.) and made strongly acid by the dropwise addition of concentrated sulphuric acid. Crude 5-benzyloxytryptamine sulphate (22.8 g., 83% yield) is filtered off, washed with ice cold water until the washings are neutral and recrystallised from water (250 ml.) incorporating a charcoal treatment. 5 - Benzyloxytryptamine sulphate monohydrate (20 g., 73% yield) is obtained as almost colourless plates, m.p. 187—189° C. (evacuated sealed tube).

Palladium chloride (0.42 g.) and acid washed charcoal (2.1 g.) are suspended in water (120 ml.) and hydrogenated at room temperature and atmospheric pressure until no further uptake occurs. A suspension of 5 - benzyloxytryptamine sulphate monohydrate (11.6 g.) in ethanol (180 ml.) is added and the resulting suspension is hydrogenated under similar conditions. An uptake of 117% of the theoretical value occurs. The catalyst and charcoal are removed by filtration through Hyflo and the filtrate evaporated to a thick syrup under reduced pressure in an atmosphere of nitrogen. The syrup is dissolved in a solution of creatinine sulphate hemihydrate (5.95 g.) in hot water (35 ml.) and to this solution is added hot acetone (250 ml.). The solid which separates is filtered off, washed with acetone and dried at 80° C. to give crude serotonin creatinine sulphate (13 g., 93% yield), m.p. 217—219° C. (sealed evacuated tube). This material is combined with two similar batches (35.8 g. in all) and the whole recrystallised twice by dissolving in hot water (300 ml.), filtering (charcoal) and adding ethanol (200 ml.). Serotonin creatinine sulphate monohydrate (25.5 g., 67% yield) crystallises on standing as almost colourless microprisms, m.p. 219—221° C. with decomposition (sealed evacuated tube).

EXAMPLE II

In a manner similar to that described in Example I, 3:4:5 - trimethoxyaniline (Hughes *et al*, Aust. J. Sci. Res. 1950 *3A*, 497) (36.6 g.) and ethyl α - acetyl - δ - phthalimidovalerate (70.0 g.) are converted to ethyl 4:5:6 - trimethoxy - 3 - (β - phthalimidoethyl)indole - 2 - carboxylate (42.0 g., 47% yield) (light brown prisms from methyl ethyl ketone, m.p. 204—206° C.) which is then hydrolysed (22.6 g.) to 4:5:6 - trimethoxy - 3 - β - (*o*-carboxybenzamido)ethylindole - 2 - carboxylic acid.

The last mentioned product may be decarboxylated without purification to give 4:5:6 - trimethoxy-3-(β-phthalimidoethyl)indole (12.0 g., 63% yield based on the phthalimidoethyl ester) (yellow needles from ethanol, m.p. 175—177° C.) which is then converted into 4:5:6 - trimethoxytryptamine which on treatment in ethanolic solution with 2N sulphuric acid gives the sulphate (colourless prisms from aqueous ethanol, m.p. 255—256° C. in a sealed evacuated tube) in a yield of 68% of theory.

EXAMPLE III

In a manner similar to that described in Example I, *p* - anisidine (24.6 g.) and ethyl α - acetyl - δ - phthalimidovalerate (69.6 g.) are converted to ethyl 5 - methoxy - 3 - (β-phthalimidoethyl)indole - 2 - carboxylate (12.2 g., 17% yield) (orange powder, m.p. 238—240° C.) which is then hydrolysed (11.1 g.) to give 5 - methoxy - 3 - β - (*o* - carboxybenzamido)ethylindole (10.6 g., 98% yield), (cream coloured powder, m.p. 244—250° C. with dehydration at 230° C.).

The last mentioned product (10.6 g.) may be decarboxylated to 5 - methoxy - 3 - (β-phthalimidoethyl)indole (7.6 g., 85.5% yield) (yellow needles from carbon tetrachloride, m.p. 156—158° C.) which is then converted (6.40 g.) to 5 - methoxytryptamine (2.35 g. 66% yield) (colourless prisms from aqueous methanol, m.p. 120—121° C.). The corresponding sulphate obtained as colourless prisms from aqueous ethanol melts at 230—232° C. in a sealed evacuated tube.

For the Applicants.

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